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Bipolar Disorder and Pregnancy: Maintaining Psychiatric Stability in the Real World of Obstetric and Psychiatric Complications

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This article describes complex, real-life issues faced by a woman with bipolar I disorder who wished to bear a healthy child while remaining psychiatrically well. The therapeutic issues include balancing treatment decisions that affect fetal and maternal risks. The authors address the importance of carefully considering the patient's history of response to medications when evaluating risks to maternal and fetal health. They discuss the role of the psychiatrist as a part of the treatment team faced with unpredictable but not unexpected complexities, such as miscarriage, abnormal or questionable prenatal screening tests, gestational diabetes, and the emergence of fetal decelerations, preterm labor, and psychiatric decompensation. The article presents and evaluates treatment decisions made in the setting of multiple obstetric and psychiatric complications that do not clearly fit published algorithms. The importance of incorporating family and social supports as an integral part of the treatment plan is emphasized.

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Bipolar disorder poses uniquely gender-specific challenges for women considering the health and well-being of their unborn children. They struggle with decisions about taking mood stabilizers and other psychiatric medications during pregnancy and whether to breastfeed their babies. Recognizing these concerns, treatment guidelines have been published to provide clinicians and patients with recommendations for moving forward to conceive and bear children in the safest way possible (1–7). While these thoughtful guidelines are based on available perinatal psychopharmacologic data, psychiatrists in tertiary centers for women with reproductive psychiatric concerns have found that in the real world of perinatal psychiatry, strict adherence to these clear and logical guidelines is not always possible. In order to maximize the likelihood that maternal mood and behavioral stability will be maintained, treating bipolar disorder during pregnancy frequently requires polypharmacy with potentially teratogenic medications that may result in adverse side effects for both mother and fetus. Women with bipolar disorder often have complicating comorbid medical conditions such as hypothyroidism and polycystic ovary syndrome that affect their fertility and their psychiatric and medical stability. Routine assessments of prolactin levels are important in bipolar women who require certain neuroleptics for stability. Not infrequently, obstetric complications such as gestational diabetes further complicate psychiatric and obstetric management. Furthermore, despite the severity of bipolar illness, decisions on whether or not to use medications are often based on the patient's wishes and available data (which are sometimes limited and sparse), resulting in relapse and ultimately the reinstatement of medications that had previously maintained the patient's clinical stability over an extended period.

This report describes the complex, real-life issues faced by a woman with bipolar disorder who was determined to do all that she could to conceive and bear a healthy child while remaining psychiatrically well. What will become clear is that using an organized algorithm derived from evidence-based data is complicated by realities confronted on a daily basis in the context of unpredictable but not unexpected variables, such as miscarriage, abnormal or questionable prenatal screening tests, gestational diabetes, and the emergence of fetal decelerations, preterm labor, and psychiatric decompensation. The importance of family dynamics and beliefs, the viability of an available support system, and education regarding preconception planning as well as the risks and benefits of using psychotropic medications during pregnancy will be discussed in the context of real-life events.

It should be noted that even when evidence-based decisions are made, clinicians and patients are often faced with newly published data that is inconsistent with prior data. The references cited below reflect both the literature available at the time of this patient's presentation and the literature published since then.

Case Presentation

Patient Description

"Ms. M" was a 29-year-old Caucasian married woman, gravida 0, with a history of bipolar disorder diagnosed at

age 18 and a history of polycystic ovary syndrome and hypothyroidism diagnosed in her early twenties. She was referred by her primary psychiatrist (W.S.R.), who had treated her for more than a decade, to the Women's Life Center, Department of Psychiatry, UCLA–Geffen School of Medicine for advice about becoming pregnant and carrying a baby to full term while remaining emotionally stable. On presentation for the initial perinatal assessment, Ms. M was euthymic and taking 400 mg/day of clozapine, 900 mg/day of lithium, and 75 mg/day of lamotrigine, as well as levothyroxine for hypothyroidism and Demulin (ethinyl estradiol and ethynodiol diacetate) for birth control. She was happily married and enjoyed her life as an advanced graduate student working on the final draft of her doctoral dissertation. She had the full support of her parents, who had devoted a great deal of time to helping her in her recovery efforts. However, Ms. M had been hospitalized psychiatrically six times during the first 2 years of her illness. After working closely with her psychiatrist and undergoing multiple medication trials over a 5-year period, she was eventually stabilized, and she had been stable for 5 years.

Ms. M and her husband, a physician, were well educated about bipolar disorder. Ms. M had excellent insight into her illness and the emotional toll it took on her family when she was severely ill. Both Ms. M and her husband, despite their desire to conceive, carry, and deliver a biological child, were deeply concerned about Ms. M's psychiatric stability during pregnancy and the effects each of the psychiatric medications she was taking might have on the safety of a developing fetus. Ms. M was also very concerned about her risk of decompensating in the postpartum period.

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History of the Present Illness

Ms. M's formal psychiatric history began when she was a college freshman. After an episode of bulimia nervosa with bingeing, vomiting, and laxative use, she experienced a severe and progressive depression. Treatment with fluoxetine was begun, but after several weeks she developed a mixed manic episode with distressing intrusive thoughts of cutting herself with knives and razors. She was unable to function at school and returned home. She was initially treated as an outpatient with beta-blockers and a benzodiazepine to address presumptive fluoxetine-induced agitation and akathisia. As her symptoms worsened, she underwent the first of multiple psychiatric hospitalizations at UCLA. A family history of bipolar disorder was obtained, and she was definitively diagnosed as having bipolar disorder, mixed state. Ms. M underwent five subsequent hospitalizations within 2 years, with major depressive episodes, severe mixed psychotic states, and serious suicide gestures and attempts, including episodes of cutting and medication overdoses. She transferred to a college closer to her family, where she began treatment with her current primary psychiatrist for both medication management and psychotherapy.

During her multiple hospitalizations, numerous medication trials were made in an effort to stabilize Ms. M's condition, including lithium, carbamazepine, sodium valproate, lamotrigine, clonazepam, fluoxetine, sertraline, citalopram, bupropion, venlafaxine, risperidone, and thiothixene. Various combinations of these medications proved to be ineffective or were associated with intolerable side effects, including flushing and eosinophilia (carbamazepine), stimulation or akathisia (fluoxetine, venlafaxine, sertraline), weight gain (most of the mood stabilizers), tremor (valproic acid and lithium), and lithium-induced hypothyroidism. During Ms. M's fifth hospitalization, ECT was administered, which brought minimal, brief improvement in her symptoms.

Because of the refractory nature of Ms. M's condition, clozapine was initiated in sequential trials of combinations with other psychiatric medications (sodium valproate, temazepam, lithium, and topiramate, as well as metformin for weight gain, stimulants for refractory depression, clomipramine for intrusive thoughts, and lamotrigine for depression). Significant and troubling side effects included weight gain of more than 20 pounds, persistent daytime sedation, and hypersomnia. Clozapine and lithium remained at the core of Ms. M's medication regimen, as these were the most effective in keeping her emotionally well.

Despite her relative stability at the time of her consultation and her strong support system, Ms. M admitted to about 12 days of moderate depression per month and occasional episodic agitation with premenstrual exacerbation. There was no history of panic disorder, substance abuse or dependence, or psychotic signs in the absence of mood symptoms.

Initial Plan

A perinatal psychiatric consultant (V.K.B.) suggested the option of surrogacy, so that Ms. M might remain on her complicated but effective medication regimen without jeopardizing the health and well-being of her fetus. Ms. M rejected this option, and instead wanted to become pregnant with the safest medications possible. The treatment

plan therefore included working closely with her primary psychiatrist to ensure that any changes in her condition would be noted quickly and addressed promptly and consulting with the perinatal psychiatrist monthly during the prepregnancy period and throughout pregnancy and the postpartum period. Psychosocial interventions were emphasized to ensure adequate rest, nutrition, and health maintenance. Permission was granted at the initial perinatal consultation to allow full dialogue with Ms. M's husband. This was essential because past history suggested that when Ms. M decompensated, she sometimes failed to alert her caregivers promptly. Because women with bipolar disorder are vulnerable to postpartum decompensation, recommendations included obtaining additional help after delivery to avoid sleep deprivation and formula feeding to ensure adequate sleep and administration of needed stabilizing medications without exposing the baby to medications through breast milk (2, 8–10).

Prior to attempting pregnancy, recommended medication changes included psychotropic agents that were thought to be safer for a fetus than were Ms. M's current medications. Because there is a relative dearth of data on clozapine in pregnancy and because clozapine has been associated with risks that include agranulocytosis, diabetes, seizures, leukopenia, and neonatal hypotonicity, it was recommended that olanzapine be cross-tapered with clozapine. At the time of Ms. M's presentation, the available literature suggested that olanzapine (an agent with which she had never been treated) was a reasonable choice for severely ill bipolar pregnant women; the literature on alternative agents, such as quetiapine and risperidone, was even more limited than that for olanzapine (2, 3, 11–13). Despite the increased risk of diabetes, the decision was made to use olanzapine to maximize mood stability (3). Because of concerns about cardiac teratogenicity with lithium, Ms. M wanted to discontinue this agent during pregnancy. Therefore, although we emphasized the severity of her illness in the early years and our concern about possible relapse, since she had done well over recent years, an attempt would be made to discontinue lithium for the first trimester of pregnancy (2, 4). After a successful cross-taper of clozapine with olanzapine, lithium would be slowly tapered and discontinued over approximately 3 months. Although the goal was for Ms. M to remain off lithium during at least the first trimester, when the fetal heart is formed, Ms. M and her husband were aware that since the absolute risk for fetal cardiac anomalies was small (approximately 1/1000), if lithium were needed to maintain psychiatric stability, it would be reintroduced (2, 4). A high-resolution ultrasound at 18 weeks' gestation and, if needed, a fetal echocardiogram, were recommended to screen for possible anomalies. Lamotrigine would be continued before, during, and after pregnancy. Folate supplementation was recommended both before and during pregnancy to reduce the risk of neural tube defects (1, 2). Assuming a successful cross-taper of clozapine with olanzapine and discontinuation of lithium followed by a 3-month period of psychiatric stability, Ms. M and her husband would then proceed to address fertility concerns posed by polycystic ovary syndrome and lithium-induced hypothyroidism under the care of a reproductive endocrinologist. They would then move forward to attempt conception.

Clinical Course

Preconception. Over the course of 2 months, clozapine was discontinued and olanzapine titrated to 20 mg/day. Fluoxetine was initiated and increased to 60 mg/day to target troubling self-deprecating obsessional preoccupations. At the time, most data suggested that fluoxetine posed no significant risk of birth defects, although we discussed with Ms. M the risk of poor neonatal adaptability with third-trimester exposure, the possible symptoms of which included jitteriness, poor muscle tone, weak cry, respiratory distress, hypoglycemia, low Apgar scores, and seizures (14–16). Other medications included lamotrigine at 150 mg/day and lithium at 900 mg/day. The daily lithium dosage was then decreased by 150 mg every 2 weeks. At a dosage of 300 mg/day, Ms. M became increasingly depressed and despondent and had fantasies about how she might kill herself. She was psychiatrically admitted with psychotic mixed mania, probably exacerbated by the introduction of fluoxetine in the absence of a therapeutic dosage of lithium. Lithium was increased to 900 mg/day, and at discharge 1 week later Ms. M had improved significantly.

Becoming pregnant. Ten months after her hospitalization, after having attained 6 months of psychiatric stability, Ms. M and her husband attempted to conceive while she continued on olanzapine, fluoxetine, lithium, and lamotrigine. On consultation with a reproductive endocrinologist, she was found to have a mildly elevated prolactin level and galactorrhea, despite treatment with olanzapine (which is less likely to raise prolactin levels than conventional antipsychotics and some other atypical antipsychotics). Treatment included micronized progesterone and clomiphene, human recombinant gonadotropin, and human recombinant follicle-stimulating hormone. Although Ms. M was taking 60 mg/day of fluoxetine, her depressive symptoms worsened, so her lamotrigine dosage was increased to 200 mg/day. Her mood improved and she proceeded with assisted fertility treatment.

Seven months after discontinuation of birth control, Ms. M became pregnant. Concurrently, just as she became pregnant, new data revealed the possible increase in congenital malformations with the use of selective serotonin reuptake inhibitors, especially paroxetine (17, 18). This information was shared with Ms. M and her husband, and there was general agreement that the risk of psychiatric destabilization if fluoxetine was discontinued was far greater than the risks of fetal malformations or perinatal difficulties. At 6 weeks' gestation, Ms. M miscarried. Genetic testing of fetal tissue revealed a chromosomal abnormality that was judged to be unrelated to medica-

tion exposure. Ms. M's depressive symptoms returned, but she responded well to an increase in her lithium dosage to 1125 mg/day and olanzapine at 25 mg/day. Using assisted reproductive technology, Ms. M became pregnant 4 months after her miscarriage.

First and second trimesters. Two ultrasound scans within the first 12 weeks of pregnancy indicated a normally developing fetus. However, a routine nuchal translucency screening test suggested a measurement at the upper limits of normal. Nuchal translucency has been used to screen for certain chromosomal abnormalities, including Down's syndrome, and for congenital structural abnormalities unrelated to Down's syndrome (including cardiac malformations). At 14 weeks, new data suggesting an association between first-trimester exposure to lamotrigine and oral clefts were shared with Ms. M and her husband (19). As the first trimester had already passed, the decision was made to continue lamotrigine treatment. (EUROCAT Antiepileptic Drug Working Group has since published data from 19 population-based registries that do not suggest an increased risk of isolated oral clefts with lamotrigine monotherapy [19, 20].) At 15 weeks, a high-resolution ultrasound scan revealed no oral clefts and a normal-looking heart. At 22 weeks, a fetal echocardiogram revealed a normal heart.

Weekly perinatal psychiatric visits involved careful monitoring of Ms. M's psychiatric condition, which was characterized by episodic dysphoria and irritability. As Ms. M moved through the second trimester, her emotional condition appeared to stabilize, although from time to time she expressed irritable depressive symptoms. Dosages of psychiatric medications were adjusted in response to changes in mood, anxiety, thought process, and behavior. Serum levels of lithium decreased over the course of pregnancy, probably in part because of an increased glomerular filtration rate and increased extracellular fluid volume consistent with a normally progressing pregnancy (1, 2). Ms. M's lithium dosage was increased to maintain therapeutic maternal serum levels. Any attempts to lower the dosage of fluoxetine below 60 mg/day resulted in increased intrusive, frightening obsessive thoughts and depressive symptoms.

By the end of the second trimester, Ms. M was experiencing fetal movements and had gained 24 pounds, and her obstetric and psychiatric conditions were judged to be normal and stable.

Third trimester. At 28 weeks, Ms. M developed gestational diabetes and was started on insulin. At 30 weeks, fetal movements ceased for several days, and obstetric examination revealed fetal decelerations and signs of placental degradation. Despite a return of fetal movements, results of a fetal nonstress test were abnormal, and Ms. M was admitted to the obstetrics unit for monitoring and expectant care. Although there was serious concern about an increased risk of bipolar relapse and it was not clear that these obstetric complications were related to the multiple psychiatric medications, Ms. M's dosages of olanzapine and fluoxetine were decreased from 20 to 10 mg/day and from 60 to 40 mg/day, respectively, and lamotrigine was discontinued. Lithium (serum level, 0.4 mEq/liter) was continued at 1350 mg/day. Betamethasone was administered to treat fetal lung immaturity to prepare for preterm birth, and fetal parameters improved. Probably in response to the reduction in psychiatric medications and the subtherapeutic level of lithium, Ms. M became increasingly depressed and had odd, intrusive thoughts of cutting her abdomen. The decision to change the psychiatric medications abruptly was made because the risk of late-term fetal demise seemed imminent, although from the perspective of preserving the patient's mental stability, it would have been better to decrease the dosages one medication at a time, if at all.

Ms. M's olanzapine dosage was once again increased, and the patient was monitored closely. Fetal parameters remained stable. Her psychiatric condition improved, and suicidal thoughts remitted. Premature rupture of membranes occurred at 36-1/2 weeks, and Ms. M delivered a baby girl by cesarean section. The infant weighed 2,608 grams and had Apgar scores of 7 and 8 at 1 minute and 5 minutes, respectively. Shortly after birth, the neonate developed transient tachypnea and was placed in the neonatal intensive care unit for observation. She did not require intubation and stabilized rapidly. After 12 hours, her breathing had normalized and she was returned to Ms. M's room with no further complications. There was no evidence of diabetes or elevated blood glucose in the neonate. She was able to suck fairly well, but she did have some occasional jerking movements over a period of 1 week, which then resolved.

Postpartum period. Ms. M had previously arranged for overnight and daily baby nurse assistance after delivery. She chose not to breastfeed because sleep deprivation was a major precipitant for mood instability and because she wanted to avoid exposing her baby unnecessarily to the multiple drugs she needed to remain emotionally stable.

Ms. M's diabetes resolved completely and she no longer required insulin. From a purely obstetric perspective, Ms. M's postpartum course was entirely unremarkable. However, during the immediate postpartum period, Ms. M became increasingly depressed and once again experienced fleeting suicidal thoughts. She questioned her ability to be an adequate mother and worried that she would never bond with her daughter. On observation, it was clear that although bonding was evident, Ms. M was extremely anxious about looking after her baby because she was experiencing troubling intrusive ruminations. Ms. M's psychiatric medications were gradually adjusted to include 450 mg of lithium each morning and 675 mg at night; 60 mg/day of fluoxetine; 200 mg/day of lamotrigine; and 20 mg/day of olanzapine. These dosages were at least as high as, and in some cases higher than, those used during pregnancy.

By 4 months postpartum, Ms. M had bonded with her baby and on most days felt competent and fully able to care for her. However, she began to experience episodic hypomanic symptoms, including anxiety, irritability, agitation, and intrusive racing thoughts. Her close relationship with both her primary psychiatrist and her perinatal psychiatrist was evident as she was able to discuss her symptoms with her treatment team and was amenable to changes in her medication regimen. In addition to a full-time baby nurse at nights, she also retained a full-time day nanny. At 7 months postpartum, olanzapine was discontinued and replaced with clozapine, and Ms. M's psychiatric condition stabilized substantially.

Infant Development

Over the course of the first year, Ms. M's infant daughter was noted to have hypotonic muscle tone. She was able to sit at 6 months, but by 1 year was unable to crawl and demonstrated continued immature muscle tone and control. Physical therapy was instituted. At 18 months, the baby was not able to walk, and evaluation by a developmental pediatrician found that gross motor skills were at the level of a 9-1/2-month-old baby. Fine motor skills and adaptive and cognitive skills were at the appropriate age level, and speech and language skills were advanced at a 20-month level with scatter to 26 months. Ms. M, her husband, and the treatment team were again faced with a complication with no clear etiology. Because a review of collateral family history revealed a history on both parental sides of delayed ambulation and problems with gross motor coordination, this was felt to be a more likely cause of motor delay than in utero exposure to medications. Continued intensive physical therapy and implementation of ankle and foot orthoses and a truncal support vest were prescribed to increase leg and core strength and coordination. The child was walking independently by 22 months, and now, at 29 months, is running and jumping. She continues to receive physical therapy, and orthotics are still used to promote further strength and coordination. It is expected that the child will fully develop, motorically, over time.

Future Plans

At 29 months, the child is developing steadily and is a happy, articulate, emotionally stable, responsive, and cognitively bright toddler. Ms. M continues to require careful psychiatric monitoring and episodically endorses symptoms of irritable depression and occasional hypomania. Nevertheless, she is a loving, intuitive, empathic, and patient mother. Ms. M and her husband have begun to think about having another baby and have sought counsel from their perinatal psychiatrist about the wisdom and feasibility of another pregnancy. Given the serious obstetric and psychiatric perinatal complications, the couple has decided that if they do have a second biological child, it will be via surrogacy, using Ms. M's egg and her husband's sperm.

Discussion

This case demonstrates some of the difficulties associated with treating women with severe mental illness who are attempting conception and pregnancy. It underscores how decisions that may improve fetal outcome can worsen maternal course. Lack of data, unpredictable response to multiple medications, and potential complications required that the treatment team be flexible in their plan, tolerate uncertainty, and educate the patient and her husband about known and potential risks at every step along the way. Key treatment components were an established, close therapeutic relationship with a long-standing primary psychiatrist; access to expert perinatal psychiatric consultation and treatment providers, such as Ms. M's obstetrician and reproductive endocrinologist, who worked closely with Ms. M and her psychiatrists; a supportive family; and financial resources that made possible close psychiatric and obstetric monitoring. Additionally, Ms. M had both the intelligence and the insight to make informed decisions regarding her treatment. Unfortunately, most women do not have such resources. Therefore, while this case presents a real patient's treatment course, women with more limited support and resources would likely face additional obstacles not addressed in this case.

Ms. M's treatment course underscores the necessity of considering a patient's history when using treatment guidelines and evaluating the potential risks of certain medications for maternal and fetal health. Ms. M had demonstrated stability on lithium after numerous failed trails on other medications. However, her strong desire to discontinue lithium in order to avoid potential cardiac teratogenicity and her long history of relative emotional stability and excellent functionality seemed to justify an attempt at prepregnancy taper and discontinuation of lithium. Especially in the presence of fluoxetine, this resulted in serious relapse, necessitating hospitalization. In retrospect, Ms. M's serious bipolar history should have precluded any attempt to discontinue lithium in preparation for pregnancy, particularly because her other primary psychiatric medication, clozapine, had been discontinued. This case also highlights the risks of substituting drugs with known effectiveness (e.g., clozapine, lithium) with drugs of unknown effectiveness (olanzapine).

Several complications, including miscarriage, lengthy hospitalization for decreased fetal movements, and the child's motoric delay, arose for which there are no clear explanations. Whether multiple psychiatric medications, many at high dosages, contributed to these events is unknown. The decision to decrease or discontinue medications to protect the fetus precipitated psychiatric decompensation. It is unknown whether hormonal or chemical factors associated with maternal illness can affect fetal development. In the setting of a background of serious psychiatric illness, it is important for the perinatal psychiatrist to emphasize that information about medications in preg-

nancy is limited and applies to monotherapy rather than polypharmacy and that there are no definitively "safe" choices when deciding on a course of action. Should complications arise, difficult decisions can be made with the help and understanding of a comprehensive treatment team. It is the parents who will live with the consequences of such decisions, and therefore informed consent with a supportive, open, and honest treatment team is essential.

More broadly, this case provokes discussion about what ethical and moral role a physician should play when a patient wants treatment that poses significant risk to her well-being and possibly the life of a child. Ms. M was firm in her initial conviction that she was not willing to consider surrogacy. At the time, she believed that carrying her baby was necessary for stable attachment. Her conflicted feelings about the risks that she and her husband took to conceive, carry, and deliver a biological child have been replaced by relief and an appreciation of how fortunate they are to have their daughter. The gross motor delay is being addressed professionally with the support and cooperation of her family, and the child has an excellent prognosis.

Women with serious medical conditions frequently become pregnant, with the full support of doctors and other caregivers. For example, women over 40, who are at high risk for complicated pregnancies and conceiving an abnormal fetus, routinely get pregnant without the extensive scrutiny of their motivations that is generally reserved for women with psychiatric illness. In contrast, for women with mental illness, stigma often precludes support from health care providers. Thus, women with bipolar disorder are often discouraged by their doctors from becoming pregnant. Although Ms. M suffers from a serious chronic psychiatric illness, she made full use of professional and psychosocial supports. She is now a responsible mother of a bright, emotionally healthy toddler.

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